Remarks

Claims 1-11, 13, 14, 16-43, 72-74, 83, 87-91, 134, 135, 137, 138, and 142 are pending. Claims 44-71, 76-82 and 92-132 have been withdrawn from consideration. Claims 12, 15, 75, 84-86, 133, 136, 139-141, 143, have been canceled. Claims 1, 13, 72, 74, 134, 135, and 138 have been amended. Support for these amendments can be found in the original claims as filed.

Rejection under 35 U.S.C. § 112, first paragraph - Enablement

Claims 1-43, 72-75, 83-91, and 133-143 remain rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants acknowledge and thank the Examiner for withdrawing the rejection of claim 1 as it applies to the alleged requirement for a promoter in the claimed constructs. However, the Office Action has maintained the rejection of the pending claims based on the scope of nucleic acids (cistrons) that encode a HEX-α or HEX-β. According to the Office Action, the specification does not reasonably enable a construct wherein the cistron encoding the HEX-α and HEX-β is a sequence other than SEQ ID NO:1 and SEQ ID NO:3, respectively.

First, the Office Action does not appear to have given due consideration to the scope of the dependent claims as evidenced by non-allowance of claim 14. Claim 14 is directed precisely to the construct considered by the Office Action to be enabled, and yet it stands rejected. Likewise, while the Office Action discusses the merits of the sequence identity claims, the majority of the arguments appear to be directed to the claims reciting HEX-α and HEX-β without reference to sequence. Furthermore, the inclusion of a functional limitation at the behest of the Examiner has apparently created the misconception that Applicants are attempting to claim the constructs based entirely on function.

Thus, in order to facilitate prosecution and place the application in better condition for allowance, Applicants have amended claims 1 and 72 to incorporate the sequence identity limitations of claims 12 and 133, respectively. As a result, the compositions are being claimed by structure based on percent identity to specified sequences. For example, the sequence for HEX-β is set forth in SEQ ID NO:3, the sequence for HEX-α is set forth in SEQ ID NO:1, and the genus of compositions is claimed based on sequence identity of these structures. For example, claim 1

as amended recites that "the HEX-β has at least 70% identity to the sequence set forth in SEQ ID NO:3 and the HEX-α has at least 70% identity to the sequence set forth in SEQ ID NO:1." Thus, the genus of compositions are varied by sequence identity to this known structure.

Second, the main point in the rejection appears to be the apparent requirement for the artisan to "resort to trial and error in order to find functional proteins." However, this is not a correct application of the enablement requirement. The test of enablement under 35 U.S.C. § 112, first paragraph is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 199 USPQ 659 (CCPA 1976)(determining enablement is a question of law based on underlying factual findings); *In re Vaeck,* 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984).

Thus, it is not the absence of experimentation that is required, the question is whether any experimentation, if necessary, is undue. Furthermore, this standard must be applied separately to the steps required to make the compositions and those required to use the composition. Thus, the present rejection depends only on the question of whether, in view of the specification and the knowledge of those of skill in the art at the time the invention was made (as evidenced by the complete record in this application), the compositions of claims 1-11, 13, 14, 16-43, 72-74, 83, 87-91, 134, 135, 137, 138, and 142 could be made and used by those of skill in the art without the need for undue experimentation.

One determines undue experimentation not by analyzing a single factor, but rather by analyzing and weighing many factors. The legal standard set out in *In re Forman* 230 U.S.P.Q. 564, 547 (Bd. Pat. App. & Int. 1986) and elucidated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988) sets forth the following factors for consideration: (1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. It is not

necessary that every enablement analysis consider all of the factors. *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

The method claims at issue in *Wands* involved the use of an antibody wherein the "antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for . . . [the antigen] of at least 10^9M^{-1}." *In re Wands*, 858 F.2d at 734. This claim covers *any* monoclonal antibody, not just a specific monoclonal antibody, and the PTO argued that the Applicant failed to enable *all* monoclonal antibodies. *Id.* Briefly, the skilled artisan generates monoclonal antibodies by injecting an antigen into a host animal causing an immune reaction, isolating spleen cells, some of which produce the antibodies that bind the antigen, fusing the spleen cells with a cancerous myeloma cell producing a hybridoma, and then screening individual hybridomas to isolate those that produce antibodies that bind the antigen. *Id.* at 733-734. The PTO supported its non-enablement position by pointing out that 1) not all hybridomas produce antibodies that bind antigen, 2) not all hybridomas that bind antigen will bind with an affinity of 10^9M^{-1}, and 3) the applicants own data indicated that a small percentage of hybridomas actually produced monoclonal antibodies which fell within the scope of the claims. *Id.* at 738-739. The court rejected these arguments by stating,

> cell fusion [hybridoma technology] is a technique that is well known to those of skill in the monoclonal antibody art, . . .[t]here was a high level of skill in the art at the time when the application was filed, and all the methods needed to practice the invention were well known . . . [and] it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened, . . .[and since] Wands carried out his entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations . . . Wands evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure.

Id. at 740.

Furthermore, the Wands court made clear that the amount of and type of experimentation considered undue fluctuates for each type of art. *Id.* The quantity of experimentation lacks relevance outside an assessment of what is "routine experimentation" in the art. *Id.* Thus, the huge amount of "experimentation" that the skilled artisan would have to perform to practice Wands' invention: immunizing an animal, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the hybridomas for

the desired characteristics, *knowing that many hybridomas would not produce functional antibodies and* ***not*** *knowing which hybridomas would produced claimed antibody*, was not undue experimentation because it was routine experimentation in the art of monoclonal antibody production. *Id.* As discussed below, the present claims and corresponding enablement rejection closely parallel the situation presented in *Wands* since the art of producing the presently claimed nucleic acid compositions encoding the genus of HEX peptides is routine experimentation in the art of recombinant nucleic acid and peptide design, even though it may seem complex.

Furthermore, the fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *See M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

Here, the claimed bi-cistronic construct covers a genus of nucleic acids encoding both HEX-β and HEX-α, wherein the HEX-β has at least 70% identity to the sequence set forth in SEQ ID NO:3 and the HEX-α has at least 70% identity to the sequence set forth in SEQ ID NO:1, wherein the HEX-β and HEX-α can form a dimer, and wherein the dimer can catabolize GM2 ganglioside.

As evidenced by "Declaration of Stephanos Kyrkanides under 37 C.F.R. § 1.132" (unsigned copy attached hereto), it is clear that the skilled artisan would, at the time the instant application was filed, 1) have a high expectation that an enzyme, such as HEX-α or HEX-β, having 70% sequence identity to the wild-type enzyme would possess at least some enzymatic activity, 2) have known to conserve a least the above amino acids (or known how to determine these amino acids) in selecting variants of HEX-α and HEX-β, and 3) have known how to test such variants for functionality (e.g., GM2 catabolysis).

With respect to teaching how to use the compositions, each of the compositions claimed must have the ability to form a dimer and catabolize GM_2 ganglioside because of the functional limitation. Furthermore, Example 6 of specification (pages 99 to 112) clearly teaches one of skill in the art how to use the claimed functional compositions. In other words, the claims only cover sequence that have the use described in the specification, and the specification teaches the skilled artisan how to use the functional compositions. It is therefore improper to assert that Applicants have not taught how to use the claimed compositions without undue experimentation.

In fact, Applicant submits that little to no experimentation is required to use the functional compositions.

Furthermore, with respect to teaching how to make the compositions, the level of skill in the art of nucleic acid synthesis and peptide synthesis and production is such that the skilled artisan would know how to make each of the sequences covered by the claim. As discussed below, each of the sequences covered by the claim are recited based on the sequence identity limitation. Thus, the skilled artisan need use only routine skill to produce each sequence and determine if it can form a dimer and catabolize GM_2 ganglioside. It is therefore improper to assert that Applicants have not taught how to make the claimed compositions.

Nevertheless, the Office Action states "[w]ithout any guidance of what region(s) within HEXA and HEXB should be avoided, in order to arrive at a functional protein, an artisan would resort to trial and error, in order to find functional proteins." However, a *prima facie* case of non-enablement is not established based solely on the potential need for experimentation in order to determine if a composition of the genus has the desired functional characteristics.

Instead, as discussed in *Wands*, there are several factors to consider in determining whether the experimentation is undue, including (1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. As discussed below, the function of the genus of enzymes is highly predictable based on the level of sequence identity to the disclosed enzymes. As such, the specification provides adequate guidance for the skilled artisan to test constructs within the genus to determine if they have the desired enzymatic property.[1] For example, the instant specification demonstrates that enzyme binding to substrate can be measured using synthetic substrates such as MU-GlcNAc and MU-FlcNac-6-SO4 (see specification page 163, line 26). Likewise, assays were known at the time the application was filed for assaying the degradation of G_{M2} gangliosides. For example, 3H-G_{M2} ganglioside and GM2 activator protein can be used to detect G_{M2} catabolysis (see Pennybacker, M., et al., 1996. J. Biol. Chem. 271(29):17377-82,

[1] Declaration of Stephanos Kyrkanides under 37 C.F.R. § 1.132, paragraph 5.

copy attached hereto). This screening process would be considered routine based on the quantity of experimentation necessary, the amount of direction or guidance presented, the presence of working examples, the nature of the invention, the state of the prior art, and the relative skill of those in the art.

Applicants have pointed to the findings of Tian and Skolnick, wherein the conservation of enzyme function was evaluated as a function of pairwise sequence identity, to demonstrate the predictability of enzyme function for sequence variants of at least 70% identity. Specifically, Tian and Skolnick evaluated the predictability of the enzyme commission (EC) number for proteins based on sequence identity. The EC number is numerical classification scheme for enzymes based on the chemical reactions they catalyze. The EC code consists of four numbers separated by periods. Those numbers represent a progressively finer classification of the enzyme, such that the fourth number generally represents the substrate specificity. Strictly speaking, EC numbers do not specify enzymes, but enzyme-catalyzed reactions. If different enzymes catalyze the same reaction, then they receive the same EC number.

The findings of Tian and Skolnick indicate that most (~90%) enzyme mutants will maintain enzyme function with sequence identities as low as 60% and in fact enzyme function does not generally *start* to diverge until the sequence identity is below 70% (See Tian and Skolnick, abstract, page 863). The lowest percent identity claimed by the Applicant is 70%, and there is no evidence, either in Tian and Skolnick or in the art, that any mutations within this range, other than the ones already known in the art to cause disease or those artisans would naturally avoid (e.g., stop codons), would in fact result in a non-functional mutant. Thus, Applicants would expect with a very high level of certainty that any given sequence would function, and the skilled artisan would rarely pick a sequence that would not function. Further, while the skilled artisan has a high expectation that any given sequence having 70% identity would function, if needed, it is routine experimentation for one skilled in the art to test such variants to determine if they fit into the claimed homology and to assay said variant for functionality (e.g., GM_2 catabolysis). Thus, as in *Wands* where the screening for IgM antibodies with a threshold binding affinity constant was determined not to require undue experimentation since the level of skill was high and the methods were well known, the assaying of candidate peptides for function, such as GM_2 catabolysis, also requires no more than routine

experimentation since there is a high level of predictability that a given peptide within the defined genus will function.

In response to this evidence, the Office Action focused on the indication by Tian and Skolnick that "functional divergence can happen at high levels of sequence identity" (page 872, col. 1, 1st paragraph) and on specific examples of proteins with high sequence identity but different substrates (Table A1, page 880). Armed with evidence that non-functional mutants can occur in homologues, the Office Action argues "[b]ecause neither the art nor the specification provide any guidance that functional divergence does not occur at high levels of sequence identity with HEXA and HEXB, an artisan cannot reasonably predict that Applicants' assertion than any mutations in HEXA and HEXB other than the ones already known would not result in a non-functional mutant." (emphasis added). Thus, the Office Action is requiring that Applicants prove a negative, i.e., that no non-functioning mutants will occur within the genus of constructs. This is clearly an unrealistic burden and not the standard for enablement. To require such would create an undue burden on the Applicants to actually test every species and identify non-functional mutants. It is sufficient that Applicants include a functional limitation to exclude from the claim those species that do not have the disclosed use.

Moreover, as seen in *Wands*, a claim is enabled when the knowledge, skill, and predictability of the art are such that the experimentation involved in testing compositions covered by the claim for the recited function is routine. As noted below, the predictability for the function of a protein having at least 70% sequence identity to a known enzyme is greater than 90%, and this assumes that no specific information regarding conserved regions of the protein are known, i.e., random mutations.[2] However, much was known about the structure-function relationship for HEX-α and HEX-β at the time the instant application was filed. For example, amino acids 1-191 and 403-529 of HEX-α and amino acid 225-556 of HEX-β were known at the time the instant application was filed to be required for G_{M2} substrate specificity (Pennybacker, M., et al.).[3]

Additionally, many of the mutations in HEX-α and HEX-β that are known to cause neurological disorders were published prior to the filing of the instant application. For example,

[2] Declaration of Stephanos Kyrkanides under 37 C.F.R. § 1.132, paragraph 3.
[3] Declaration of Stephanos Kyrkanides under 37 C.F.R. § 1.132, paragraph 4

mutations in HEX-α that were known to result in Tay-Sachs disease include a 4bp insertion in exon 11; 2bp deletion in exon 5; intron mutations; early termination codons; and Glu482Lys, 1510delC, Arg178His, Arg178Cys, Gly269Ser, Arg504His, Arg499His, Arg170Gln, Trp420Cys, Gly250Asp, Phe304Del, Arg504Cys, Ser210Phe, Arg137Ter, Arg393Ter, TRP26Ter, Arg178Leu, Met1Val, Arg499Cys, Trp329Ter, Trp485Arg, Tyr180Ter, Arg247Trp, Val192Leu, Val200Met, Asp258His, Arg170Trp, Lys197Thr, Phe211Ser, Leu127Arg, His204Arg, Met301Arg, Cly454Ser, Leu39Arg, Trp392Ter, Gly805Ala, Tyr180His, Trp474Cys, Leu451Val, and Val324Val mutations (see OMIM[4] database # 606869). Likewise, mutations in HEX-β that were known to result in Sandhoff's disease include a 16-kb deletion of the promoter, exons 1 through 5, and part of intron 5; intron mutations; and Tyr456Ser, Pro417Leu, Lys121Arg, Arg505Gln, Pro405Leu, Ala543Thr, Ser62Leu, Pro504Ser, and 76delA mutations (see OMIM database # 606873). As many of these disease-causing mutations were already known, the skilled artisan would have known at the time this application was filed to conserve a least the above amino acids in selecting variants of HEX-α and HEX-β.

Thus, Applicants have provided evidence for a high probability that enzymes will maintain substrate specificity based on 70% sequence identity, and the Office Action has provided no reasonable basis to dismiss this general expectation. Rather, it has attempted to rely on exceptional examples to shift the burden to Applicants to prove the absence of divergence for HEX proteins, i.e., to prove a negative, which is not a reasonable expectation. Applicants therefore submit that instead of providing a *prima facie* case for non-enablement, the Examiner has instead attempted to require that Applicants provide a *prima facie* case for enablement. This is clearly improper.

Applicants note that, while there is a high predictability for sequence variants of at least 70% identity, claim 73 alternatively recites 80% sequence identity, claim 135 alternatively recite 85% sequence identity, and claims 138 and 142 alternatively recite 95% sequence identity. Applicants therefore request that these alternative scopes be given due consideration in light of the quantity of experimentation necessary, the amount of direction or guidance presented, the

[4] OMIM™ - Online Mendelian Inheritance in Man™ (http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM) is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.

presence of working examples, the nature of the invention, the state of the prior art, and the relative skill of those in the art.

Accordingly, the Applicant respectfully requests the withdrawal of the rejection, and allowance of claims 1-11, 13, 14, 16-43, 72-74, 83, 87-91, 134, 135, 137, 138, and 142.

Rejection under 35 U.S.C. § 112, first paragraph - Written Description

Claims 1-43, 72-75, 83-91, and 133-143 remain rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the Examiner states that "nothing in the specification or the art indicate what region(s) of HEX-α or HEX-β is the domain(s) that provide the activity of catabolizing GM_2, such that an artisan could reasonably predict that targeting certain residues would affect enzymatic activity" and that "screening for these mutants based on enzymatic activity is not adequate written description."

The courts have clearly established that the first paragraph of 35 U.S.C. § 112 includes, *inter alia*, two separate requirements: (1) an enablement requirement based on the statutory language that the application describe "the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same," and (2) a written description requirement based on the statutory language "[t]he specification shall contain a written description of the invention" (the third requirement of the first paragraph of 35 U.S.C. § 112, the "best mode" requirement, is not relevant here). The separate status of the make and use clause and the written description clause was at the heart of the recognition of the separate written description requirement. *See Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1560-61 (Fed. Cir. 1991); *Enzo Biochem v. Gen-Probe*, 285 F.3d 1013, 1018, 1021 (Fed. Cir. 2002) (hereafter "*Enzo I*")).

The essential goal of this written description requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed. *See In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. *See The Regents of the*

University of California v. Eli Lilly and Co., 119 F.3d 1559, 1566; 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) (hereafter, "*Lilly*").

Lilly is often cited to support a written description rejection of claims to genetic sequences, because it established that an adequate written description for genes requires more than the name of the gene and a statement of its function, it "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Lilly*, 119 F.3d at 1566; 43 USPQ2d at 1404. However, the courts have for the most part limited the holding in *Lilly* to the facts of that case. For example, the Federal Circuit rejected the idea that written description requires a disclosure of structure for DNA inventions. *See Enzo Biochem, Inc. v. Gen-Probe Inc.* (*Enzo II*), 323 F.3d 956 (Fed. Cir. 2002)(finding that deposit of DNA sequences satisfied written description for a claim to subsequences and variants of the sequences). In fact, the Federal Circuit appears to have further limited the relevance of *Lilly* to "new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." *Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003). Consistent with this, the Federal Circuit has stated that it does not require patentees to recite known DNA structures, i.e., does not require a re-description of what was already known. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006).

The Patent Office undertook a review of the written description caselaw in view of *Lilly* in order to establish guidelines for the examination of patent applications for compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. *See Guidelines for Examination of Patent Applications Under 35 U.S.C. 112, ¶1 "Written Description" Requirement*, 66 Fed. Reg. 1,099 (Jan. 5, 2001) (hereafter, "*Written Description Guidelines*"). Far from requiring any absolute or *per se* requirement for adequate written description, the resulting *Written Description Guidelines* provide a case-specific and fact-dependant inquiry. This is consistent with caselaw, where compliance with the written description requirement is consistently referred to as a fact-dependent inquiry. *See, e.g., Vas-Cath v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991).

"Actual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a

composition structurally ... in such a way as to distinguish the composition with particularity from all others." *Written Description Guidelines,* Response to Comment 7, pg. 1101.

"If an adequate description is provided, it will suffice 'whether located among the original claims or in the descriptive part of the specification.'" *Written Description Guidelines,* Response to Comment 17, pg. 1102, citing *In re Gardner*, 480 F.2d 879, 880, 178 USPQ 149 (CCPA 1973).

"If a complete structure is disclosed, the written description requirement is satisfied for that species or embodiment, and a rejection under 35 U.S.C. § 112, ¶ 1, for lack of written description must not be made." *Written Description Guidelines,* pg. 1106.

The USPTO has already established that variants can be claimed based on sequence identity (see Example 14 of the U.S.P.T.O. "*Synopsis of Application of Written Description Guidelines*")(hereinafter "*Synopsis*"), wherein it is stated:

> [t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants...which are capable of the specified catalytic activity.

(*Synopsis*, page 54, fourth paragraph). Thus, the *Guidelines* and *Synopsis* specifically sanction the use of percent identity claims of reasonable scope. However, examiners do not appear to be following this direction, and this activity has led to a number of reversals at the Board of Patent Appeals and Interferences (BPAI).

The BPAI has been very consistent when it comes to written description rejections of percent identity claims. A recent review of decisions by the BPAI revealed six cases where the Board reversed an examiner's written description rejection of a percent identity claim, and not a single instance where such a rejection was affirmed.

Most notably, in *Ex parte Sun,*[5] the examiner pointed out that the patent specification failed to disclose a single example of a wee1 variant retaining the activity of wee1 and sharing only 80% identity with the reference sequence, and "argued that the 'specification does not set forth what specific structural or physical features define the claimed isolated nucleic acids,'" and

[5] Appeal No. 2003-1993, Application No. 09/470,526 (B.P.A.I.)(not written for publication)

"that one skilled in the art could not predict the structure and function of isolated nucleic acids comprising a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1.'" *Id.* at 7-8. The Board noted however that "predictability is not the legal standard or test for [written description] rejections" and dismissed the examiner's argument that the specification failed to teach a single representative species within the genus. The Board therefore reversed the written description rejection, citing *Enzo II* and holding that the disclosure of the single reference sequence and methodology for screening for variants having Wee1 activity was sufficient to satisfy the written description requirement. *Id.* at 8-9, 11. *See also Ex parte Bandman,*[6] *Ex parte Au-Young,*[7] *Ex parte Meyers,*[8] *Ex parte Bandman,*[9] and *Ex parte Smith.*[10]

The Examiner supports the instant rejection by citing MPEP § 2163, stating "[a] patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." The MPEP supports this position by citing *In re Curtis* (*Curtis*), 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004), wherein claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss. However, *Curtis* is not contrary to the present claims.

The instant claims are clearly distinguishable from those in *Curtis*, where the artisan could not predict the operability of <u>any</u> species other than the one disclosed. In contrast, the ordinary artisan most definitely can predict additional species that would be operable for the instant claims. In fact, conservative mutations are highly predictable ways to change the sequence of an amino acid without affecting structure and/or function. As such, there are at least thousands of predictable variants based on single amino acid substitutions. In fact, a computer program could print each and every sequence meeting these requirements, but surely the PTO is

[6] Appeal No. 2003-1805, Application No. 09/079,892 (B.P.A.I.)(not written for publication)
[7] Appeal No. 2003-1817, Application No. 09/501,714 (B.P.A.I.)(not written for publication)
[8] Appeal No. 2003-1820, Application No. 09/464,039 (B.P.A.I.)(not written for publication)
[9] Appeal No. 2004-2319, Application No. 09/915,694 (B.P.A.I.)(not written for publication)
[10] Appeal No. 2005-0147, Application No. 10/203,081 (B.P.A.I.)(not written for publication)

not asserting that this must be done for patentability. Thus, *Curtis* is not properly applied to the instant claims. As the Office Action has not provided any reasonable evidence to the contrary, it is improper to conclude that Applicants were not in possession of the full genus of claimed constructs on this basis.

The Examiner further cites MPEP § 2163, which states that "[a]n adequate written description also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed." (emphasis provided). The MPEP supports this position by citing *Univ. of Rochester v. G.D. Searle & Co.* (*Rochester*), 358F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004), noting that the patent at issue provided only a description of assays for screening compounds to identify those that could be used in the claimed method.

However, the instant claims do not attempt to define the composition with only a wish or plan as in *Rochester*. In *Rochester*, the claims were directed to a method of using a Cox-2 inhibitor wherein no inhibitor had yet been identified or disclosed in the application. The court determined that the application lacked adequate written description for these inhibitors. This is clearly not analogous to the instant claims. The above argument would only be valid if the claim were to a composition comprising a nucleic acid encoding any protein that catabolizes GM_2 ganglioside, i.e., with no structural limitation. Such a claim would be attempting to describe the composition entirely by function and/or by a means of identifying compositions having that function. In contrast, the present claims are limited to nucleic acids encoding HEX-β and HEX-α having at least 70% identity to the sequence set forth in SEQ ID NO:3 and at least 70% identity to the sequence set forth in SEQ ID NO:1, respectively. Applicants are not attempting to describe the genus based on a function or a method of identifying the compositions. The fact that the skilled artisan may have to test a construct within the genus to verify function is not equivalent to defining the construct by function. In contrast, the construct is clearly defined based on its structure and a function is provided in the specification to allow the artisan to verify its utility.

Furthermore, as set forth in the *Guidelines*, written description can be satisfied by defining a genus of genetically related compositions by their sequence identity. The only thing to determine is the extent of the sequence identity that should be allowed in any given case. As

argued above, the Applicants believe they are entitled to the full scope of 70% sequence identity. As noted above in the *Synopsis*, a single species can be representative of a genus where all members have at least 95% sequence identity with the reference compound. This is based on the presumption that the skilled artisan would conclude that the Applicant was in possession of the necessary common attributes possessed by the members of the genus. *See Id.* However, if the existence of the function of members of a genus having at least 70% sequence identity with the reference compound is no less predictable, then the skilled artisan would be no less inclined to assume that the Applicant was in possession of the necessary attributes possessed by the larger genus. This is where Tian comes into play, as discussed above. Thus, satisfaction of the written description requirement, i.e., possession of the genus of compounds, is a sliding scale that is determined by the predictability that the reference compound is in fact representative of the genus. Applicants believe they have provided sufficient evidence that, absent evidence to the contrary, a specific amino acid sequence for a given enzyme should be considered representative of a genus of members having at least 70% sequence identity with the reference compound. However, to facilitate prosecution, claim 73 alternatively recites 80% sequence identity, claim 135 alternatively recite 85% sequence identity, and claims 138 and 142 alternatively recite 95% sequence identity. Applicants point out that claims 73, 135, 138 and 142 require an even closer structural relationship to the reference sequence. Thus, the predictability and understanding by those of skill in the art of what Applicants were in possession of at the time of filing would be even more certain and unquestionable. Thus, Applicants request that these alternative scopes be given due consideration.

Accordingly, the Applicant respectfully requests the withdrawal of the rejection, and allowance of claims 1-11, 13, 14, 16-43, 72-74, 83, 87-91, 134, 135, 137, 138, and 142.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment authorizing payment in the amount of $930.00, representing $525.00 for the fee under 37 C.F.R. § 1.17(a)(3) for a Three Month Extension of Time and $405 for the fee under 37 C.F.R. 1.17(e) for a Request for Continued Examination; a Request For Continued Examination pursuant to 37 C.F.R. § 1.114, a Request For Extension of Time, a copy of Pennybacker, M., et al. (1996. J. Biol. Chem. 271(29):17377-82), and Declaration of Stephanos Kyrkanides under 37 C.F.R. § 1.132 (unsigned) are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No.14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Brian Giles

P. Brian Giles
Registration No. 57,896

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

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I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.			
Name of Person Mailing (Print/Type)	P. Brian Giles, Ph.D.		
Signature	Brian Giles	Date	12-20-2007